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## **Case Report**

### **Minimal Change Disease: A Case Report of an Unusual Relationship**

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**ABSTRACT.** Kidney injury associated with lymphoproliferative disorders is rare, and the exact pathogenetic mechanisms behind it are still poorly understood. Glomerular involvement presenting as a nephrotic syndrome has been reported, usually secondary to membranoproliferative glomerulonephritis. We report a case of a 63-year-old male who presented with bilateral leg swelling due to nephrotic syndrome and acute kidney injury. A kidney biopsy showed minimal change disease with light chain deposition; however, no circulating light chains were present. This prompted a bone marrow biopsy, which showed chronic lymphocytic leukemia (CLL) with deposition of the same kappa monoclonal light chains. Three cycles of rituximab and methylprednisolone resulted in remission of both CLL and nephrotic syndrome, without recurrence during a three-year follow-up.

#### **Introduction**

Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children but it may occur in adults as well. Although nephrotic syndrome can be associated with a number of solid and hematological malignancies,<sup>1-5</sup> the association with chronic lymphocytic leukemia (CLL) is unusual. There

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are only 18 reported cases of MCD with CLL in the medical literature,<sup>4-8</sup> and only one of these patients had documented circulating monoclonal light chains,<sup>6</sup> we report a case of MCD with kappa light chain deposition in the mesangium without detectable urinary or serum light chains. The nephrotic syndrome responded to the treatment of CLL with rituximab and methylprednisolone.

#### **Case Report**

The patient is a 63-year-old Caucasian male with a history of coronary artery disease, heart failure with preserved ejection fraction, hypertension, and chronic kidney disease with a

baseline serum creatinine of 1.5 mg/dL. He presented to our hospital with shortness of breath and lower extremity edema. On initial examination, he was in no distress, blood pressure 187/95 mm Hg, pulse 90 beats/min, and O<sub>2</sub> saturation was 95% on 2 L nasal cannula. He had bilateral basal crackles and soft pitting pedal edema up to the knees. The remainder of the examination was unremarkable. Laboratory data showed a mild elevation of his creatinine to 1.74 mg/dL, mild thrombocytopenia 120,000 with a normal white blood cell count (WBC) of 7800/ $\mu$ L with normal differential count. Hemoglobin was 12.9 g/dL at this time. His urine dipstick showed 3+ protein. His serum albumin was 2.5 g/dL. His lipid profile was normal except for elevated triglycerides at 204 mg/dL. A random urine estimated his protein excretion to be 9.7 g/day. Renal ultrasound showed asymmetry with a small kidney on the right. As a result, a renal biopsy was canceled and he was placed on methylprednisolone 48 mg/day for the idiopathic nephrotic syndrome and discharged home. He had an initial response with a fall in urinary protein to 1.5 g/day and improvement in his edema.

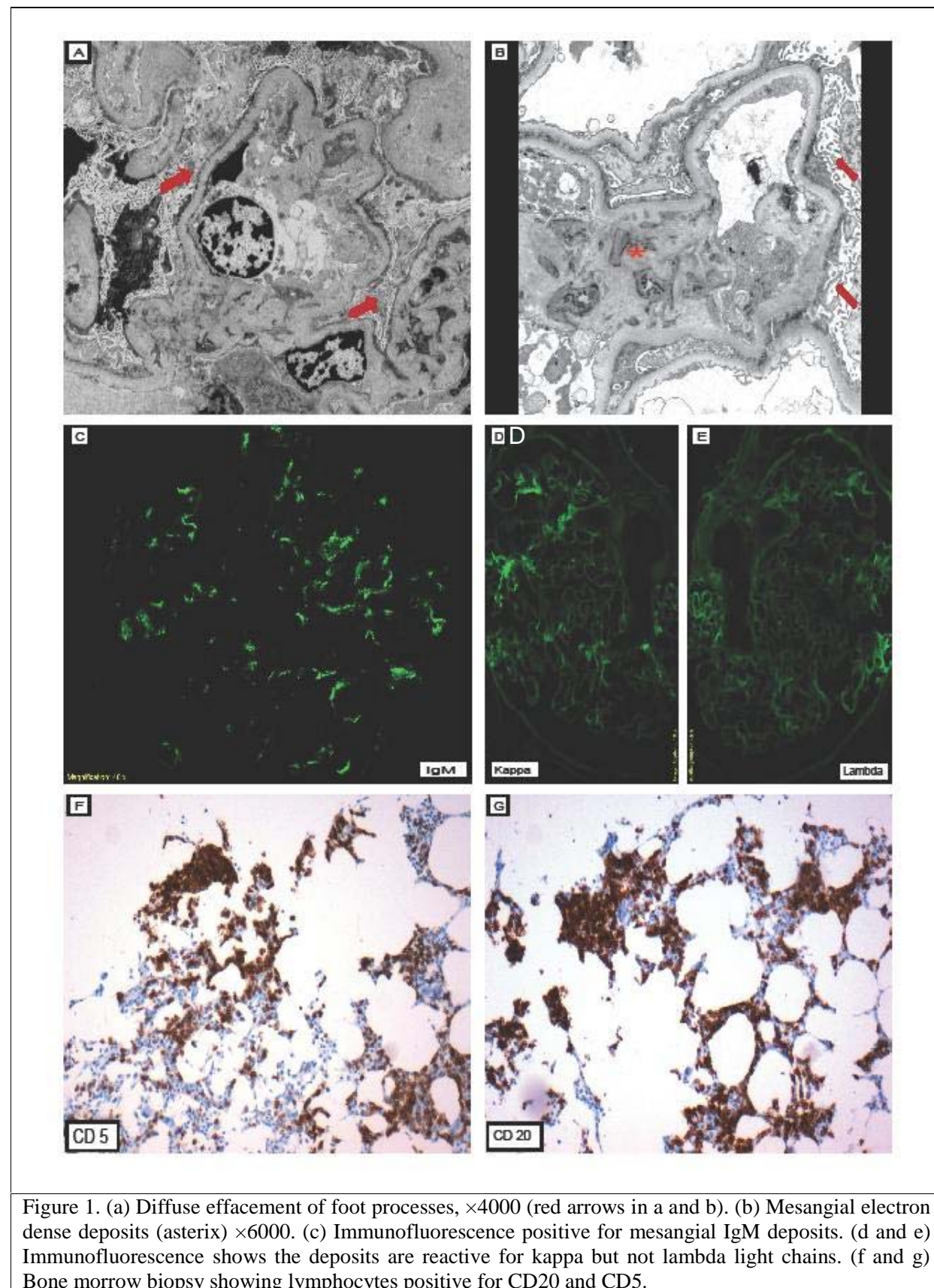
At two months, he presented with worsening proteinuria and edema despite continuing the same dose of methylprednisolone with which he was compliant by history. Cyclosporine was added to his regimen. Serum creatinine increased to 5.2 mg/dL following one day of cyclosporine administration, which was markedly higher compared to 1.43 mg/dL three weeks earlier. Urine sediment showed lipid and abundant granular casts. Other abnormal tests included BUN 174 mg/dL, hemoglobin (Hgb) 9.3 g/dL, and platelet count 152,000  $\mu$ L, which fell to 82,000  $\mu$ L three days later. WBC remained normal. His renal function continued to worsen and hemodialysis was initiated. At this time, he underwent a percutaneous renal biopsy which on electron microscopy showed diffuse foot process effacement and scattered small electron dense deposits present within the mesangial matrix (Figure 1a and b). Immunofluorescence microscopy showed the segmental granular deposition of IgM (2+/4+),

kappa light chains (2+/4+), no lambda light chain reactivity, and trace C3 in the mesangial areas (Figure 1c-e). Both serum and urine immunofixation performed on two separate occasions were negative. Free light chain ratio was normal at 0.89 (normal 0.26–1.65). Because of the IgM kappa deposits, he underwent a bone marrow biopsy. The bone marrow aspirate and biopsy showed a B-cell monoclonal population that was CD5, CD20, and CD23 positive (Figure 1f and g) with surface IgM kappa immunoglobulin, representing 34% of bone marrow cellularity, which was diagnostic of CLL. Cytogenetics and fluorescence *in situ* hybridization (FISH) studies showed that the B lymphocytes had a deletion of 13q and trisomy 12, characteristically associated with CLL.

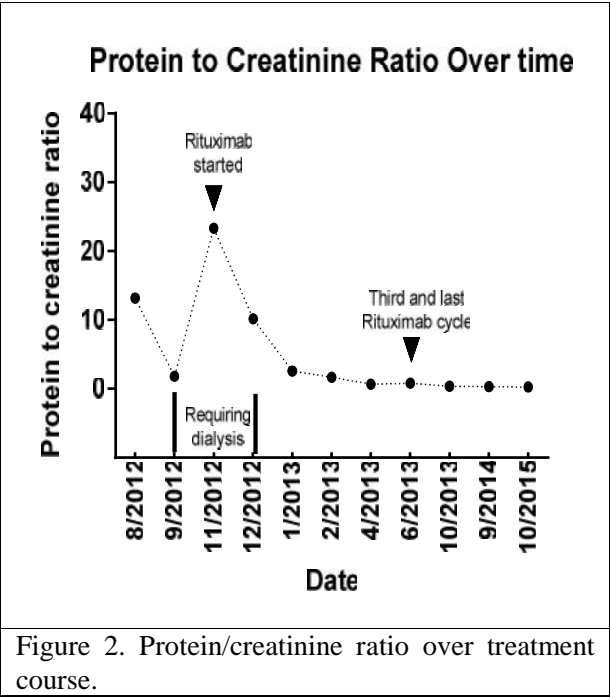
Based on these findings, treatment with rituximab 375 mg/m<sup>2</sup> once a week for four weeks and methylprednisolone 1 g/m<sup>2</sup> on the first 3 days of the week was initiated. After three cycles, his nephrotic syndrome improved (urine protein excretion below 500 mg/day) and his serum creatinine fell below 2 mg/dL; he no longer required dialysis (Figure 2). The Hgb and platelets increased to 13.2 and 153,000, respectively. He has remained in remission from nephrotic syndrome and CLL for over three years without further treatment. However, he developed hypogammaglobulinemia most likely secondary to rituximab treatment with IgA 20 mg/dL (normal 81–463 mg/dL), IgG 125 mg/dL (normal 694–1618 mg/dL), and IgM <1 mg/dL (normal 48–271 mg/dL). This has resolved after two years of conservative management.

## Discussion

This is an unusual case of MCD secondary to underlying CLL with no hematologic manifestations other than bone marrow and renal involvement. The main clue to a hematological disorder as the cause was the IgM kappa deposition in the mesangium on renal biopsy. While IgM nephropathy, evident by IgM mesangial deposits on kidney biopsy, is a common pattern of MCD, especially in children







and is usually associated with steroid resistant or steroid dependent nephrotic syndrome.<sup>9</sup> Staining is usually positive for both kappa and

lambda. In contrast to the case of Alzamora,<sup>6</sup> a monoclonal protein was not detected in the blood or urine of our patient. Identifying mesangial deposition of monoclonal light chains on renal biopsy in minimal chain disease should trigger a search for an underlying lymphoproliferative disorder. The acute kidney injury was attributed to acute tubular necrosis, which has been observed in MCD<sup>10</sup> and was unlikely to be due to one day of cyclosporine administration.

Of the 18 previously reported cases of CLL with MCD, treatment was reported on 13 of the patients (Table 1). Most were treated with corticosteroids alone or in combination with chlorambucil. Two of the previous cases were treated with rituximab, one as initial treatment and the other as second line after steroid plus chlorambucil failed.<sup>5</sup> Resolution of the nephrotic syndrome occurred in the first case but not the second. While rituximab has been used successfully to treat idiopathic MCD,<sup>16,17</sup> the deposition of monotypic immunoglobulin on

Table 1. Cases of chronic lymphocytic leukemia and minimal change disease that reported data about treatment and outcome (13 cases).

| Author                             | Number of cases | Treatment                                 | Outcome   |
|------------------------------------|-----------------|---|---|
| Kerkhoven 1973 <sup>11</sup>       | 1               | Cs  | Remission of NS   |
| Seney 1986 <sup>12</sup>           | 2               | Chlor<br>Cs                               | Minimal decrease in serum creatinine<br>Remission of NS then relapse with renal insufficiency |
| Farrant 1988 <sup>13</sup>         | 1               | Cs followed by several courses of chlor   | Remission of NS   |
| Vivaldi 1992 <sup>14</sup>         | 1               | Cs  | Increase lymphocyte   |
| Spalding 2001 <sup>15</sup>        | 1               | Methylprednisolone, 2 cycles of COP       | Improved proteinuria, WBC, and creatinine   |
| Alzamora 2006 <sup>6</sup>         | 1               | Cs and Chlor                              | Remission of NS, normalized WBC count   |
| Kofman 2014 <sup>5</sup>           | 4               | Cs  | Relapsed then remission after the second Cs course  |
|                                    |                 | Cs then Chlor. R/Cs then F/Cs for relapse | No resolution of proteinuria with all treatments  |
|                                    |                 | Cs  | Relapsed then remission of NS after the second Cs course                                      |
| Poitou-Verkinder 2015 <sup>8</sup> | 2               | Cs then R                                 | Remission of NS   |
|                                    |                 | No treatment<br>Cs followed by chlor/Cs   | Persistent NS<br>Relapse that responded to chlor/Cs   |

NS: Nephrotic syndrome, WBC: White blood cell, Cs: Corticosteroid, Chlor: Chlorambucil, R: Rituximab, F: Fludarabine, COP: Cyclophosphamide, vincristine, and prednisone.

biopsy supports a secondary form of the disease. The treatment of the underlying cause has been associated with resolution of the nephrotic syndrome in this setting. The combination treatment of rituximab with methylprednisolone is an effective treatment for CLL and is well tolerated.<sup>18</sup> A major side effect of rituximab is hypogammaglobulinemia,<sup>19</sup> which necessitates careful follow-up to detect infections early.

### Conclusion

The major significance of our case is that it brings to light the importance of aggressively pursuing the etiology of MCD in patients with nephrotic syndrome with immunoglobulin deposition, even when serum and urine immunofixation and the WBC are normal.

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**Conflict of interest:** None declared.

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